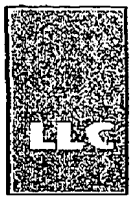

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COMMENTS: ☒ Urgent ☐ To your revision ☒ Reply urgently ☐ Please, comments

Concerns: PCT/BR03/00076

Dear Sirs,

In append follows the amendments in accordance with Article 19 about the international application number **PCT/BR03/00076** by the applicant CRISTÁLIA PRODUTOS QUÍMICOS FARMACÊUTICOS LTDA.

Sincerely,

Douglas Vieira Pinto
Industrial Property Agent

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INDUSTRIAL PROPERTY AND TECHNOLOGICAL & SCIENTIFIC INFORMATION CONSULTING

Rio de Janeiro, January 26, 2004.

To:
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Cco:
COMMISSIONER OF PATENTS AND TRADEMARKS
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY
Box PCT
Washington, D.C. 20231 - EUA
Telephone: 0021 (1 703) 308-1235
Facsimile: 0021 (1 703) 305-3230

SUBJECT: FILLING OF AMENDMENTS AND STATEMENT UNDER ARTICLE 19.

In response of the INTERNATIONAL SEARCH REPORT, mailed on 01 DEC 2003, about the international application number **PCT/BR03/00076** by the applicant CRISTÁLIA PRODUTOS QUÍMICOS FARMACÊUTICOS LTDA., we are sending the amendments on the claims conform the **article 19**.

In view of the applicant already done the demand of the international preliminary exam, we are sending a copy of this letter to the IPEA/US.

Cordially,

Douglas Vieira Pinto
Industrial Property Agent
LLC Info Connecion Ltda..

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REPLY TO THE INTERNATIONAL SEARCH REPORT

Reply to PCT International Search Report
Amendments under Article 19
PCT/BR03/00076

To:
International Bureau of WIPO,
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Sir:

Responsive to the "Notification of Transmittal of the International Search Report or the Declaration" of December 01, 2003, please enter the following amendments into the file of the above-identified application.

In order to satisfy the requirement of PCT Rule 4.3, the original title "SOLUBLE STABLE PHARMACEUTICAL COMPOSITION FOR THE ADMINISTRATION OF HIV PROTEASE INHIBITORS AND A PROCESS FOR THE PREPARATION OF CONCENTRATED PHARMACEUTICAL COMPOSITIONS FOR THE ADMINISTRATION OF HIV PROTEASE INHIBITORS" was replaced by "PHARMACEUTICAL COMPOSITION AND PROCESS FOR PREPARING CONCENTRATE PHARMACEUTICAL COMPOSITION". The amended title is shorter and precise.

Where originally there were 31 claims and after amendments of some claims there are 36:

- Original claims 1 and 2 were replaced by amended claims bearing the same number [for correcting minor grammatical and/or spelling errors];
- Original claim 3 was subdivided into amended claims 3 and 4 [for eliminating the double ranges in the same claim and correcting punctuation mark];
- Original claim 4 was subdivided into amended claims 5 and 6 [for eliminating the double ranges in the same claim, correcting punctuation mark and clarifying the subject);
- Original claim 5 was subdivided into amended claims 7 and 8 [for eliminating the double ranges in the same claim, correcting punctuation mark and clarifying the subject];

- Original claim 6 was subdivided into amended claims 9 and 10 [for eliminating the double ranges in the same claim, correcting punctuation mark and clarifying the subject];
- Original claim 7 was subdivided into amended claims 11 and 12 [for eliminating the double ranges in the same claim and clarifying the subject];
- Original claims 8 to 20 were replaced by the amended claims 13 to 25 [for correcting minor grammatical and/or punctuation mark errors and/or clarifying the subject];
- Original claims 21 to 31 were replaced by the amended claims 26 to 36 [for correcting minor grammatical and/or spelling errors and/or clarifying the subject].

No new mater was introduced by any one of the amended claims.

Respectfully submitted,

Douglas Vieira Pinto
Industrial Property Agent
LLC Info Connecion Ltda..

INTERNATIONAL APPLICATION PCT/BR03/00076 WITH THE RESPECTIVE AMENDMENTS

AMENDED CLAIMS

1. Pharmaceutical composition characterized by comprising:

(a) a therapeutic amount of the protease inhibitor [5S-(5R*,8R*,10R*,11R*)]-10 - hydroxy - 2 - methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)- 4 - thiazolyl] - 3,6 - dioxo - 8,11 - bis (phenylmethyl) - 2,4,7,12-tetraazatridecan-13-oic acid 5-thiazolylmethyl ester (ritonavir);

(b) a mixture of alcoholic solvent and alcoholic co-solvent of C_2-C_4;

(c) a mixture of medium chain mono/diglycerides of C_8-C_{10};

(d) a pharmaceutical suitable surfactant;

(e) an antioxidant.

2. Pharmaceutical composition in accordance with claim 1, characterized by optionally comprising:

(a1) an emulsion stabilizer;

(b1) a polarity corrector.

3. Pharmaceutical composition in accordance with claim 1, characterized by employing the protease inhibitor [5S-(5R*,8R*,10R*,11R*)]-10 - hydroxy - 2 - methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)- 4 - thiazolyl] - 3,6 - dioxo - 8,11 - bis (phenylmethyl) - 2,4,7,12-tetraazatridecan-13-oic acid 5-thiazolylmethyl ester (ritonavir) in a concentration ranging from 1.0% to 60% in weight of the final composition.

4. Pharmaceutical composition in accordance with claim 3, characterized by employing the protease inhibitor [5S-(5R*,8R*,10R*,11R*)]-10 - hydroxy - 2 - methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)- 4 - thiazolyl] - 3,6 - dioxo - 8,11 - bis (phenylmethyl) - 2,4,7,12-tetraazatridecan-13-oic acid 5-thiazolylmethyl ester

(ritonavir) in a concentration ranging from 10% to 50% in weight of the final composition.

5. Pharmaceutical composition in accordance with claim 1, characterized by the alcoholic solvent is used in a concentration ranging from 5.0% to 20% in weight of the final composition.

6. Pharmaceutical composition in accordance with claim 5, characterized by the alcoholic solvent is used in a concentration ranging from 5.0% to 15% in weight of the final composition.

7. Pharmaceutical composition in accordance with claim 1, characterized by the alcoholic co-solvent is used in a concentration ranging from 5.0% to 20% in weight of the final composition.

8. Pharmaceutical composition in accordance with claim 7, characterized by the alcoholic co-solvent is used in a concentration ranging from 5.0% to 15% in weight of the final composition.

9. Pharmaceutical composition in accordance with claim 1, characterized by the alcoholic solvent and the alcoholic co-solvent are used in a concentration ranging from 10% to 40% in weight of the final composition.

10. Pharmaceutical composition in accordance with claim 9, characterized by the alcoholic solvent and the alcoholic co-solvent are used in a concentration ranging from 10% to 30% in weight of the final composition.

11. Pharmaceutical composition in accordance with claim 1, characterized by the medium chain mono/diglycerides mixture of C_8-C_{10} is used in a concentration ranging from 20% to 80% in weight of the final composition.

12. Pharmaceutical composition in accordance with claim 11, characterized by the medium chain mono/diglycerides

mixture of C_8-C_{10} is used in a concentration from 20% to 70% in weight of the final composition.

13. Pharmaceutical composition in accordance with claim 1, characterized by the surfactant is used in a concentration ranging from 0.1% to 20% in weight of the final composition.

14. Pharmaceutical composition in accordance with claim 1, characterized by the antioxidant is used in a concentration ranging from 0.001% to 2.0% in weight of the final composition.

15. Pharmaceutical composition in accordance with claim 1, characterized by the alcoholic solvent is ethanol and the alcoholic co-solvent is propylene glycol.

16. Pharmaceutical composition in accordance with claim 1, characterized by the surfactant is polyethoxylated castor oil 35, and/or hydrogenated polyethoxylated castor oil 40, and/or polysorbates 20, 40, 60 or 80.

17. Pharmaceutical composition in accordance with claim 1, characterized by the antioxidant is butylated hydroxy toluene and/or alpha-tocopherol.

18. Pharmaceutical composition in accordance with claim 1 or 2, characterized by employing an emulsion-stabilizing agent in an concentration ranging from 0% to 60% in weight of the final composition.

19. Pharmaceutical composition in accordance with claim 1 or 2, characterized by the emulsion-stabilizing agent is polyethylene glycol 400 (PEG 400).

20. Pharmaceutical composition in accordance with claim 1 or 2, characterized by employing a polarity corrector agent in a concentration ranging from 0% to 0.5% in weight of the final composition.

21. Pharmaceutical composition in accordance with claim 1 or 2, characterized by the polarity corrector agent is citric acid and/or ascorbic acid.

22. Pharmaceutical composition in accordance with any one of claims 1-21, characterized by being employed for oral administration as an oral solution, hard gelatin capsules and/or soft gelatin capsules.

23. Pharmaceutical composition in accordance with claim 22, characterized by being employed for oral administration as soft gelatin capsules.

24. Pharmaceutical composition in accordance with any one of claims 1-21, characterized by being employed in the treatment of viral infections.

25. Pharmaceutical composition in accordance with any one of claims 1-21, characterized by being employed in medicine or veterinary.

26. Process for preparing soluble concentrate pharmaceutical compositions of [5S-(5R*,8R*,10R*,11R*)]-10 - hydroxy - 2 - methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)- 4 - thyazolyl] - 3,6 - dioxo - 8,11 - bis (phenylmethyl) - 2,4,7,12-tetraazatridecan-13-oic acid 5-thiazolylmethyl ester (ritonavir), comprising the following steps:

(a2) dissolving [5S-(5R*,8R*,10R*,11R*)]-10 - hydroxy - 2 - methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)- 4 - thiazolyl] - 3,6 - dioxo - 8,11 - bis (phenylmethyl) - 2,4,7,12-tetraazatridecan-13-oic acid 5-thiazolylmethyl ester (ritonavir), in a sufficient amount of an alcoholic solvent of C_2-C_4, under controlled temperature;

(b2) eliminating solid particles by filtration;

(c2) evaporating the alcoholic solvent, under reduced pressure at low temperature, to about half of its initial concentration;

(d2) adding an alcoholic co-solvent, a medium chain mono/diglycerides mixture, an antioxidant, an emulsion-stabilizing agent and a polarity corrector in the appropriate amounts for the composition;

(e2) removing the alcoholic solvent by distilling under reduced pressure until the remaining quantity is the desired quantity in the composition;

(f2) adding the surfactant under continuous stirring and keeping stirring until complete mixture;

(g2) correcting the composition final weight by adding the alcoholic solvent employed in the initial dissolution of ritonavir, if necessary.

27. Process in accordance with claim 26, characterized by the alcoholic solvent in (a2) is ethanol.

28. Process in accordance with claim 26, characterized by the step (a2) is conducted in a temperature ranging from 30°C to 45°C.

29. Process in accordance with claim 26, characterized by the step (c2) is conducted at a maximum temperature of 40°C.

30. Process in accordance with claim 26, characterized by the co-solvent is propylene glycol.

31. Process in accordance with claim 26, characterized by the medium chain mono/diglycerides mixture is a mixture of medium chain mono/diglycerides of C_8-C_{10}.

32. Process in accordance with claim 26, characterized by the antioxidant is butylated hydroxy toluene or alpha-tocopherol.

33. Process in accordance with claim 26, characterized by the emulsion-stabilizing agent is polyethylene glycol 400 (PEG 400).

34. Process in accordance with claim 26, characterized by the polarity corrector is citric acid or ascorbic acid.

35. Process in accordance with claim 26, characterized by the surfactant is polyethoxylated castor oil 35, and/or polyethoxylated hydrogenated castor oil 40, and/or polysorbates 20, 40, 60 or 80.

36. Process in accordance with claim 26, characterized by being employed in the preparation of concentrated pharmaceutical compositions of ritonavir for oral administration.